Excerpts from a larger submission by the Animal Health Institute relating to Pathogen Load Studies. Submission of April 5, 1999 to FDA Docket No. 98D-1146, "A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals."

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Pathogen Load Studies

Historically, information provided by Dr. Diane Fagerberg of C.A.R.E. indicates that through 1992 there have been a total of 21 different feed additive antimicrobials tested in a total of 52 studies (29 salmonella shedding and 23 antibiotic resistance in cattle, swine and poultry). The majority of antimicrobials "passed." There were, however, a few that "failed," or were presumed to have failed, and the data was never submitted to CVM because the project was abandoned by the sponsor. There is no database on antimicrobials that have been administered by other routes, doses, or durations. Prior to requiring pathogen load studies for all product usages, a careful evaluation should be undertaken to ensure that these studies will provide the type of information the CVM anticipates.

The stated assumption in the Framework Document is that the pathogen load in an animal is predictive of the amount of human foodborne illness that is observed. There has been concern that the traditional "558.15" studies do not meet this goal, yet it appears that similar studies are to be developed anyway. Implicit in the requirement for a "pathogen load" study, is the assumption that quantitative viable counts of pathogens, above a baseline norm, will present a greater risk to public health. No evidence exists (that AHI is aware of) that correlates increased on-farm gut concentration or prevalence of foodborne pathogens to increased human disease from those pathogens. Perhaps if one goes to an extreme situation might the correlation become valid, but incrementally elevated counts would be problematic. Thus, while HACCP practices seek to reduce pathogens incrementally at each step of the food processing chain (farm to fork) to fall within a pre-determined tolerable range, there is no established threshold or tolerance for on-farm pathogen "loads." Furthermore, without some demonstration of the correlation between on-farm data and human disease, it is questionable as to what value the acquisition of such data will have in providing the CVM with information to evaluate a product candidate's safety.

There are a number of inherent difficulties that can be pointed out if one attempts to acquire such information to establish the relationship. The 1995 NAHMS swine survey provides

ample evidence of the multifactorial nature of the issue and highlights the confounding factors that preclude the establishment of a causal relationship.

On-farm surveys showed that fecal salmonella was present in 38% of operations, but regional variation was evident with a range of 30% in the midwest and 65% in the southeast. Larger herds had a higher prevalence of salmonella than smaller herds (57% vs. 32%). Not all pens on all farms tested positive for salmonella; in fact most pens were negative. There was a sex effect with single sex pens twice as likely as mixed sex pens to be positive. Only 6% of the finisher pens were salmonella positive, indicating that salmonella was shed sporadically at low levels. Ten serotypes accounted for 85% of the isolates. Of the serotypes isolated, only 4 were on the CDC's top ten list of human pathogens but in a non-related order. In other words, *S. agona* was the #2 isolate for swine, but #6 from humans; *S. typhimurium* was #6 from pigs, but #2 from humans; *S. heidelberg* was # 7 in swine, but #3 in man; and *S. enteritidis* BA was #9 from pigs and #1 in man. *From this limited survey, it should be clear that the establishment of a pathogen load relationship will be nearly impossible owing to a host of confounding factors, many of which are not related to antibiotic use.* Not specifically mentioned above is the effect of isolation media on recovery rates, seasonality, vaccinations (against salmonella), etc. but this is discussed in the full text NAHMS document.

Even allowing for "best practice" management on-farm, the final process of slaughter can compromise the microbiological safety of the animals. It is known that transportation stress causes increased shedding of salmonella, even from previously culture negative animals. Withdrawal of feed can also produce a similar result. Cross-contamination of animals with fecal material can also result in a few "shedders" spreading pathogens to other animals in the pen or cage. No amount of on-farm hygiene, short of raising the animals in a sterile or SPF environment, can eliminate this possibility.

A second objective of the pathogen load studies is to determine the effects of mitigation measures on resistance development. It is not clear as how this is to be done. It seems as though the Framework urges that mitigation studies should be done in tandem with pathogen load studies, in anticipation that the pathogen load studies will "fail." What mitigation efforts are envisioned; *e.g.*, irradiation of carcasses, extended observation periods post-medication, feed withdrawal or addition prior to transport to slaughter, etc.? Is there the potential that these human microbial safety-related study requirements could dictate animal drug withdrawal times or proscribe certain usage restrictions? What would constitute a universally acceptable, practical and effective mitigation measure? Until such time as additional information on the value and design of conducting mitigation measure studies is available, it is impossible to know what to do to comply with this objective.

For these reasons, the value and relevance of conducting pathogen load studies is questionable. The practicality of obtaining meaningful data from on-farm studies also needs to be assessed.

Sources of confusion relating to Pathogen Load studies

The definition of "pathogen load" is not clearly specified in the Framework Document. Although salmonella, campylobacter, and *E. coli* O157 are listed as pathogens early in the document, Footnote 1 indicates that the definition is basically animal enterics that cause human disease. Other general descriptions of what the study should include are found scattered throughout. For example, in the paragraph prior to Section III, an increase in the bacteria that can cause human infections or prolonging the duration of the carrier state of such bacteria are parenthetically referred to as pathogen load. In Section IV under the heading of Pathogen Load, it refers to pathogen load "at the time of slaughter." In the paragraph on the "M" exposure category in the section discussing pre-approval studies, the Framework Document refers to pathogen load being reduced prior to slaughter, yet in the paragraph on "H" exposure, it says that the amount of time required for the pathogen load to decrease would need to be determined.